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Early age at start of antiretroviral therapy associated with better virologic control after initial suppression in HIV-infected infants

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Abstract

Objective—The report of the “Mississippi baby” who was initiated on antiretroviral therapy (ART) within 30 hours of birth and maintained viral suppression off ART for 27 months has increased interest in the timing of ART initiation early in life. We examined associations between age at ART initiation and virologic outcomes in five cohorts of HIV-infected infants and young children who initiated ART before 2 years of age in Johannesburg, South Africa.

Methods—We compared those who initiated ART early (<6 months of age) and those who started ART late (6–24 months of age). Two primary outcomes were examined: (1) initial response to ART in three cohorts and (2) later sustained virologic control after achieving suppression on ART in two cohorts.

Results—We did not observe consistent differences in initial viral suppression rates by age at ART initiation. Overall, initial viral suppression rates were low. Only 31, 40.1, and 26.5% of early-treated infants (<6 months of age) in the three cohorts, respectively, were suppressed <50 copies/mL of HIV-RNA 6 months after starting ART. We did observe better sustained virologic control after achieving suppression on ART among infants starting ART early compared to late.

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Conflict of Interest

The authors have no conflicts of interest to report.

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Children who started ART early were less likely to experience viral rebound (>50 copies/mL or >1000 copies/mL) than children who started late in both cohorts.

Conclusions—These findings provide additional support for early initiation of ART in HIV-infected infants.

Keywords

antiretroviral therapy; early treatment; viral suppression; virologic control; infant

Introduction

Evidence from the Children with HIV Early Antiretroviral Therapy (CHER) randomized clinical trial in South Africa and other observational studies indicates that initiation of antiretroviral therapy (ART) early in life reduces morbidity and mortality in HIV-infected infants [1–5]. These findings have informed treatment guidelines which now advise initiation of ART irrespective of clinical and immunological status in all HIV-infected infants and children [6–8]. The report of the “Mississippi baby” who was initiated on antiretroviral therapy (ART) within 30 hours of birth and who maintained viral suppression off therapy for 27 months [9] has further stimulated interest in the possible benefits of initiating ART soon after birth.

Data on the effects of the timing of early ART initiation on virologic outcomes, including initial virologic response and sustained virologic control after suppression are limited. Some studies have reported better initial virologic response in children started on ART <3–6 months of age compared to children started after 6 months of age [4, 10] while others have reported no differences in short-term suppression rates [11, 12]. Reports of infants started on ART in the first months of life with no comparator group of children started at older ages have shown varied rates of initial suppression [13–16]. Few studies have compared later virologic control, *i.e.* maintenance of suppression without rebound after achieving initial suppression, between children initiating ART at earlier versus later ages. One study of children who initiated ART younger or older than one year of age and who achieved virologic suppression found no association between age at ART start and rebound of HIV-RNA >400 copies/mL at later ages [17].

With increasing attention to the possible benefits of ART initiation in newborns, it is important to investigate the effects of the timing of ART initiation on virologic response in larger cohorts in sub-Saharan Africa where the vast majority of new pediatric infections occur [18]. Here, using data from five study cohorts of HIV-infected children initiating ART before 2 years of age in Johannesburg, South Africa, we examine the association between age at starting ART and (1) initial viral response in three cohorts and (2) later virologic control after achieving suppression in two cohorts.

Methods

Study populations

Five cohorts of HIV-infected infants and young children in Johannesburg, South Africa were included in this analysis (Table 1). Three cohorts of children initiating ART (Cohorts A, B, and C.1) were suitable to examine the association between age at ART initiation and initial response to treatment. Two cohorts of children who had achieved virologic suppression after ART initiation (Cohorts C.2 and D) were suitable to assess the association between age at ART initiation and later virologic control.

Cohort A included newly-diagnosed, treatment-naïve HIV-infected infants and young children identified at hospital admissions, prevention of mother-to-child transmission (PMTCT) follow-up visits, and immunization services as part of an active surveillance study intended to improve engagement in care and ART initiation at three hospitals and two affiliated clinics conducted between January and December 2011 [19–21]. We restricted the analysis to 219 children known to have been initiated on ART before 2 years of age. At enrollment into the surveillance study (pre-treatment), blood samples were collected from each child for plasma HIV-RNA tests (Roche Taqman HIV Test v2.0) and CD4 percentage. Sociodemographic and clinical information was also collected. Subsequent information on survival, HIV-RNA, and CD4 percentage, as close as possible to 6 months post-ART initiation, was abstracted from medical records.

Cohort B included 718 newly-diagnosed, treatment-naïve infants and young children who initiated ART before 2 years of age as part of public HIV services at the Empilweni Services and Research Unit at Rahima Moosa Mother and Child Hospital (RMMCH) between January 2004 and July 2012 and who had at least one follow up visit after ART initiation or died after ART initiation. At this time ritonavir-boosted lopinavir (LPV/r)-based was given to children in this age group and viral load testing was recommended every 6 months after ART initiation [22]. Demographic information, age at ART initiation, HIV-RNA, and CD4 percentage were extracted from a routine database maintained by the site for clinical care purposes.

Cohort C.1 consisted of 323 newly-diagnosed, treatment-naïve infants and young children enrolled into the pre-randomization phase of an ART strategies trial that took place at RMMCH from April 2005 to June 2010 [23]. All children had been exposed to nevirapine used for PMTCT given to the mother, to the child, or both and were initiated on LPV/r-based ART before 2 years of age. Blood samples for plasma HIV-RNA quantification (Roche version 1.5 Amplicor assay, Roche, Branchburg, NJ) and CD4 percentages were measured before treatment began and at 4, 12, 24, 36, and 52 weeks after treatment initiation as part of the pre-randomization phase.

Cohort C.2 includes all 195 of the children from Cohort C.1 who met criteria for randomization (HIV-RNA <400 copies/mL for at least 3 months within the first 12 months of treatment) and were assigned to remain on LPV/r (N=99) or switch to nevirapine (N=96) (ClinicalTrials.gov: NCT00117728) [24, 25]. Children undergoing randomization after viral suppression had been achieved (a median of 9 months after ART initiation) had additional

blood samples collected at scheduled post-randomization visits (4, 16, 24, 36, and 52 weeks).

Cohort D included children 3–5 years of age with a history of nevirapine exposure for PMTCT who were suppressed on LPV/r (HIV-RNA <50 copies/mL at the time of enrollment into the study) and randomized to either remain on LPV/r or switch to efavirenz as part of an ART strategies trial that took place at RMMCH from June 2010 to December 2013 (ClinicalTrials.gov: NCT01146873) [26]. This analysis was limited to 293 children who initiated ART before 2 years of age, including 145 children randomized to remain on LPV/r and 148 randomized to switch to efavirenz. Plasma HIV-RNA (AmpliPrep/COBAS® TaqMan® HIV Test, version 2.0, Roche, Branchburg, NJ) measurements were obtained at randomization and scheduled post-randomization visits (4, 8, 16, 24, and 48 weeks). CD4 percentage was measured at study entry and 24 and 48 weeks post-randomization.

Studies were approved by the Institutional Review Boards of Columbia University (New York, New York) and the University of the Witwatersrand (Johannesburg, South Africa). Signed informed consent for all procedures and data was provided by each child's guardian for Cohorts A, C.1, C.2, and D and for data sharing for Cohort B.

Statistical analysis

To examine effects of the timing of ART initiation, we compared children who initiated ART <6 months of age to those who started ART 6–24 months of age. The <6 months age category was refined further in some analyses. Two primary virologic outcomes were examined: (1) initial response to ART and (2) later sustained virologic control after achieving suppression on ART.

Initial response to ART was examined in Cohorts A, B, and C.1. HIV-RNA (categorized as <50, 50–1000, 1000 copies/mL) measured around 6 months post-ART initiation was compared between age at ART initiation groups. We defined the window for “6 months” to be between 3 and 12 months. If more than one result was available, the result nearest to 6 months was chosen. Secondary outcomes for Cohorts A, B, and C.1 included CD4 percentage as a continuous and as a categorical variable (<10, 10–15, and ≥15) at 6 months post-ART initiation. Vital status by 6 months post-ART initiation was also determined.

Later virologic control after suppression on ART was assessed in Cohorts C.2 and D. The proportion of children in three HIV-RNA categories (<50, 50–1000, 1000 copies/mL) at scheduled visits post-randomization was compared between age at ART initiation groups. A generalized estimating equation (GEE) model with an unstructured correlation structure was used to examine the overall effect of age at ART initiation on HIV-RNA outcomes at repeated visits. Other correlation structures produced similar results. We adjusted for treatment randomization group (LPV/r vs. nevirapine in Cohort C.2; LPV/r vs. efavirenz in Cohort D).

Additionally, we compared area under the plasma viral load curve (AUVLC), a measure of “cumulative viral load,” between age at ART initiation groups. The AUVLC in log₁₀ copy-weeks/mL at scheduled visits in the two cohorts was calculated using the trapezoidal rule,

whereby larger areas indicate higher cumulative viremia [27]. The data were normalized so that a child with an AUCVL of 0 was considered fully suppressed and a child with a detectable AUCVL was not fully suppressed at follow-up visits.

Statistical comparisons were conducted using chi-squared or Fisher's exact tests for categorical variables, ANOVA and t-tests for normally-distributed continuous variables, and Kruskal-Wallis tests for non-normally distributed continuous variables. All *p*-values are 2-tailed and *p*-values <0.05 were considered statistically significant. Analyses were performed using SAS version 9.4 (Cary, North Carolina, USA).

Results

Characteristics

Characteristics of the children included in this study are shown in Table 2 stratified by cohort. Cohort A included infants who were actively identified to improve engagement in care and ART initiation and Cohort B included infants accessing routine clinical services. Cohorts C.1, C.2, and D were comprised of infants enrolled in clinical trials. Sex distribution and pretreatment characteristics, including HIV-RNA, CD4 count and percentage, and WAZ were similar across the cohorts. Mean age at ART initiation ranged from 8.7 months in Cohort A to 10.5 months in Cohort B. A higher proportion of children in Cohort A (47.5%) and Cohort D (46.4%) initiated ART early (i.e. <6 months of age) than Cohort B (35.1%), Cohort C.1 (31.6%), and Cohort C.2 (27.7%).

Initial response to treatment

Pre-treatment, a higher proportion of children starting ART early (<6 months) had higher HIV-RNA levels (>750,000 copies/mL) than children starting ART late (6–24 months of age) in all three cohorts (Table 3). Pre-treatment CD4 percentage was consistently higher in the early initiators and the proportion of children underweight (WAZ <-2) was lower in children starting ART early compared to late in Cohort A only (Table 3).

Post-treatment, it was only in Cohort A that children who initiated ART early were more likely to be suppressed (<50 copies/mL) at 6 months than children who initiated ART late. This was not observed in Cohorts B and C.1 (Table 3). In a finer stratification of age at ART initiation in Cohort A, the proportions of children suppressed <50 copies/mL 6 months post-ART initiation were 35.5, 25.9, and 9.8% in those who started ART <3 months, 3–6 months, and 6–24 months, respectively. This trend was not seen in Cohorts B and C.1. Adjustment for pre-treatment viral load or other pre-treatment characteristics including sex, CD4 percentage, and WAZ did not change these results (data not shown). When the three cohorts were combined, there was no difference in suppression to <50 copies by 6 months for children who initiated ART early (<6 months) vs. late (6–24 months), even after adjustment for pretreatment HIV-RNA and CD4 percentage (OR=0.99, 95% CI: 0.71, 1.39).

In Cohorts A, B, and C.1 the mean CD4 percentage at 6 months post-ART initiation was higher in children who initiated ART early (Table 3) but after adjustment for pretreatment CD4 percentage in all three cohorts, the difference was no longer statistically significant (*p*=0.087, 0.403, 0.201). There was a trend towards lower mortality among children treated

<6 months vs treated 6–24 months in Cohort A ($p=0.076$) (Table 3). In a further stratification of age at ART initiation categories into <3 months, 3–6 months, and 6–24 months, the proportions of children who died by 6 months post-ART initiation were 4.6, 16.4, and 20.2% respectively in Cohort A ($p=0.006$). No differences between age at ART initiation groups in the proportion of deaths was observed in Cohorts B and C.1.

We combined the data from the three cohorts to investigate effects of the timing of ART initiation in monthly increments in the first 6 months of life. No clear trends in the proportion of children suppressed by 6 months post-ART initiation were observed by age at ART initiation in months. The percentage of children suppressed <50 copies/mL ranged from 25% to 49.3% across all age intervals in months of age at ART initiation (Table S1).

Later virologic control

Age at ART start influenced later virologic control after viral suppression in both Cohorts C.2 and D. Of 195 children in Cohort C.2, children <6 months at ART start were less likely to have a plasma HIV-RNA 50–1000 copies/mL and plasma HIV-RNA >1000 copies at all scheduled post-randomization visits than children 6–24 months at ART start (Figure 1). In a GEE model accounting for repeated visits, the odds of having an HIV-RNA 50–1000 vs. <50 copies/mL was lower in children who initiated ART early compared to children who initiated ART late, adjusted for randomization group (OR=0.34, 95% CI: 0.19, 0.61). A similar trend was seen in the GEE model for having an HIV-RNA >1000 vs. <1000 copies/mL (OR=0.29, 95% CI: 0.08, 1.11).

Of 293 children in Cohort D, children <6 months at ART start were less likely to have a plasma HIV-RNA 50–1000 copies/mL at all but one scheduled post-randomization visit than children 6–24 months at ART start. There were no consistent differences in the proportion of children with HIV-RNA >1000 copies/mL by age at starting ART but HIV-RNA >1000 copies/mL was rare in both groups (Figure 1). In a GEE model, the odds of having an HIV-RNA 50–1000 copies/mL vs. <50 copies/mL for children who initiated ART early was 0.46 times that of children who initiated ART late, adjusted for randomization group (OR=0.46, 95% CI: 0.24, 0.87).

In Cohort C.2, a smaller proportion of the children who started treatment early had a detectable AUVLC compared to children who started treatment late (30.0 vs. 50.7%, $p=0.012$) across all scheduled trial visits. Among those with a detectable AUVLC, children starting treatment early had a lower median log₁₀ copy-weeks/mL than children starting treatment late (1.7 vs. 9.5, $p=0.03$). Similarly, in Cohort D, a smaller proportion of the children who started treatment early had a detectable AUVLC compared to children who started treatment late (19.1 vs. 31.9%, $p=0.013$) across all scheduled trial visits. Among those with a detectable AUVLC, there was no difference in median log₁₀ copy-years/mL between children starting ART early and late (Figure 2).

Discussion

We did not observe a consistent benefit of early ART initiation on rates of initial viral suppression in the first 6 months of treatment in three non-overlapping cohorts from

Johannesburg, South Africa. In one of the three cohorts we observed better virological suppression by 6 months in children who initiated ART compared to those who initiated 6–24 months but no differences were observed in the other two. Pre-treatment viral loads and CD4 percentages in all three cohorts were higher in children younger at ART initiation, consistent with the natural history of HIV infection in infancy [28–31]. However, even after accounting for these differences, in a combined analysis of the three cohorts, there were no significant differences in initial viral suppression between children starting treatment early and late. The higher pre-treatment viral loads suggest that the rate of decline was more rapid in the early-treated groups but truncation in the upper range of the assays in use at the time limited our capacity to measure this directly.

While the better virologic response in children initiating ART early observed in Cohort A is encouraging, the lack of confirmation in the other two cohorts leads us to suspect that other factors may be involved. Cohort A was a surveillance study which was intended to actively identify mothers and infants not already engaged in care. These children were predominantly identified through hospital admissions and, in particular, more children starting ART early (<6 months) were identified through routine PMTCT services. Hence these children may have had less advanced disease and benefit most from early treatment than children in the other cohorts starting treatment early. There was some evidence to suggest this speculation may be valid, as pre-treatment weight-for-age Z-scores, a sensitive marker of disease progression, were slightly better in children starting treatment early in Cohort A compared to the other two cohorts. Better surveillance systems in place to identify HIV-infected infants in order to initiate ART at an early age may improve initial outcomes. A prior study has also reported higher rates of viral suppression <500 copies/mL by 6 months in those starting ART 3 months of age compared to those starting treatment 3–12 months of age (63 vs. 19%, $p<0.001$) [10]. Another study reported more early treated infants (<6 months of age) reaching undetectable viral load than later treated infants (6–52 months of age) over a median follow up time of 4.1 years (73.3 vs. 30.1%, $p<0.0001$) [4]. Two other studies reported no differences in initial virologic suppression at 6 months between children starting early and late [11, 12].

Of note, overall rates of initial viral suppression at 6 months were low. Only 31, 40.1, and 26.5% of early-treated infants in Cohorts A, B, and C.1, respectively, were suppressed <50 copies/mL at 6 months after starting ART. The large proportion of infants at risk for viral failure is concerning, particularly since options for second-line regimens are limited for children.

In children who had initially achieved suppression, we observed a consistent benefit of early ART initiation on rates of sustained viral suppression in the two cohorts we examined. Compared to children who started treatment later in infancy and early childhood (6–24 months of age), children who started treatment early (<6 months) were less likely to experience viral rebound and had a lower cumulative viral load in follow up than children who started treatment later. This benefit was observed in both cohorts and across the different treatment regimens (nevirapine, efavirenz and LPV/r) that were evaluated in these two trials. Although age at ART initiation (<1 year vs. >1 year) in older children who achieved virologic suppression was not associated with rebound of HIV-RNA >400

copies/mL in one study [17], other studies have reported better long-term virologic control in infants starting ART at an early age. In a group of 20 children from the CHER trial maintained on suppressive ART for 7–8 years, 9/12 (75%) of children starting ART before 2 months of age had undetectable plasma HIV-RNA compared to 3/8 (37.5%) of infants who started after 2 months of age ($p=0.17$) [32]. A study of HIV-infected children maintained on ART for up to 18 years and virally suppressed on conventional assays found plasma viremia by ultrasensitive assays to be below the limit of detection (<2 copies/mL) in all four children who initiated ART early (before 3 months of age) but detectable (median 8 copies/mL) in all four children who did not initiate ART until later childhood (6–15 years) [33].

HIV infection requires life-long ART because of its persistence in latent viral reservoirs located in long-lived resting memory CD4+ T cells and other anatomic sanctuaries that harbor dormant replication-competent proviruses [34, 35]. ART targets replicating virus and has not been shown to eradicate these replication-competent HIV reservoirs. The establishment of the latent viral reservoir occurs early during primary infection [36], and evidence in adults supports that early initiation of ART close to the time of HIV acquisition may limit HIV reservoir size [37–39] and lead to HIV remission in certain adults, termed post-treatment controllers [40, 41]. In infants, several reports have indicated that early ART initiation limits the size of the viral reservoir [13, 32, 42, 43]. A study of 17 HIV-infected infants starting treatment in the first 6 months of life found a significantly smaller viral reservoir in infants treated before 6 weeks of age compared to children initiating ART between 6 weeks and 6 months of age [13]. Although eradication of HIV with early ART has not yet been shown to be feasible, treatment early in life with sustained adherence may restrict the size of the viral reservoir, thereby reducing the likelihood of viral rebound, as demonstrated in this study, and increasing the possibility for sustained suppression with potent ART.

Our study had limitations. Our analysis used a 6 month cut off for early ART initiation, but even earlier age intervals are important to investigate. In all of our cohorts, there were only small numbers of children initiating ART before 6 weeks of age, too few for a subgroup analysis. In addition, although we combined data from three cohorts in our evaluation of initial response to treatment, we were unable to account for differences in viral load assays as well as changes in drug regimens, dosing, and clinical practice taking place in the time period during which children were enrolled.

In conclusion, our study demonstrates improved virologic control after initial viral suppression in children starting ART before 6 months of age compared to those starting at 6–24 months in two large cohorts. We did not find consistent benefits of early treatment on initial viral suppression. Our results suggest that there are virological benefits of early treatment in addition to those shown for reduction of mortality and morbidity [1, 2], growth [44], and neurological outcomes [45]. These results provide additional impetus for early initiation of ART in HIV-infected infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Cohort C.2: **Cohort D:** **Figure 1.**

Percentage of children with plasma HIV-RNA 50–1000 copies/mL (cpm) and VL ≥ 1000 cpm at scheduled trial visits in Cohort C.2 and Cohort D by age at antiretroviral therapy (ART) initiation (<6 months vs. 6–24 months)

Figure 2. Percentage not suppressed (a,c) and median area under the viral load curve (AUVLC) (b,d) at intervals between scheduled trial visits in Cohort C.2 and Cohort D, respectively, by age at antiretroviral therapy (ART) initiation (<6 months vs. 6–24 months)

Description of five cohorts of HIV-infected infants and young children initiating antiretroviral therapy (ART) before 24 months of age

Table 1

Cohort	Relevant citations	N	Years	Brief description	Purpose – to examine:
Cohort A	[19–21]	219	2011	Newly-diagnosed, treatment-naïve infants and young children identified as part of a surveillance study	Initial viral response
Cohort B	NA	718	2004–2012	Newly-diagnosed, treatment-naïve infants and young children initiating ART at a routine HIV clinic	Initial viral response
Cohort C.1	[23]	323	2005–2010	Newly-diagnosed, treatment-naïve infants enrolled into pre-randomization phase of ART strategies trial and initiated on LPV/r-based ART (ClinicalTrials.gov: NCT00117728)	Initial viral response
Cohort C.2	[24, 25]	195	2005–2010	Children from Cohort C.1 who met criteria for randomization (plasma HIV-RNA <400 copies/mL for at least 3 months within the first 12 months of treatment) and were assigned to remain on LPV/r or switch to nevirapine as part of an ART strategies trial (ClinicalTrials.gov: NCT00117728)	Later virologic control
Cohort D	[26]	293	2010–2013	Children 3–5 years of age who were suppressed on LPV/r (plasma HIV- RNA <50 copies/mL at the time of enrollment into the study) and randomized to remain on LPV/r or switch to efavirenz as part of an ART strategies trial (ClinicalTrials.gov: NCT01146873)	Later virologic control

Characteristics of five cohorts of HIV-infected infants and young children initiating antiretroviral therapy (ART) before 24 months of age

Table 2

Characteristic	Cohort A	Cohort B	Cohort C.1	Cohort C.2	Cohort D
N	219	718	323	195	293
Sex, N (%)					
Male	104 (47.5)	351 (49.0)	168 (52.0)	104 (53.3)	137 (46.8)
Female	115 (52.5)	366 (51.1)	155 (48.0)	91 (46.7)	156 (53.2)
PMTCT exposure, %	69.0%	Unknown	100%	100%	100%
Age at ART initiation (months), Mean $\pm$ SD					
<6 months	8.7 $\pm$ 6.5	10.5 $\pm$ 6.7	10.1 $\pm$ 5.8	10.0 $\pm$ 10.7	8.9 $\pm$ 6.4
6–12 months	104 (47.5)	252 (35.1)	102 (31.6)	54 (27.7)	136 (46.4)
12–24 months	56 (25.6)	202 (28.1)	115 (35.6)	69 (35.4)	79 (27.0)
	59 (26.9)	264 (36.8)	106 (32.8)	72 (36.9)	78 (26.6)
Pretreatment HIV-RNA quantity (copies/mL), N (%)					
<100000	22 (10.8)	83 (15.8)	25 (8.8)	19 (11.0)	33 (13.7)
100000–750000	64 (31.5)	157 (29.8)	78 (27.6)	58 (33.5)	75 (31.1)
750000	117 (57.6)	287 (54.5)	180 (63.6)	96 (55.5)	133 (55.2)
Missing	16	191	40	22	52
Pretreatment CD4 count (cells/mm ³), Mean $\pm$ SD	1260 $\pm$ 1193	985 $\pm$ 802	1006 $\pm$ 754	1063 $\pm$ 704	1213 $\pm$ 793
Pretreatment CD4 percentage, N (%)					
<10	32 (15.0)	91 (16.6)	55 (18.1)	26 (14.0)	32 (11.7)
10–15	33 (15.5)	106 (19.3)	61 (20.1)	37 (19.9)	51 (18.6)
15	148 (69.5)	353 (64.2)	188 (61.8)	123 (66.1)	191 (69.7)
Missing	6	168	19	9	19
Mean $\pm$ SD	22.5 $\pm$ 12.6	19.2 $\pm$ 10.1	18.5 $\pm$ 9.1	19.1 $\pm$ 8.5	21.7 $\pm$ 10.6
Pretreatment weight-for-age z-score (WAZ), Mean $\pm$ SD	-2.20 $\pm$ 1.9	-2.53 $\pm$ 2.4	-2.49 $\pm$ 1.7	-2.18 $\pm$ 1.7	-2.16 $\pm$ 1.6
WAZ <-2, N (%)	118 (55.4)	345 (62.8)	169 (58.3)	91 (51.7)	106 (52.7)
N Missing	6	169	33	19	92

Characteristic	Cohort A	Cohort B	Cohort C.1	Cohort C.2	Cohort D
Treatment Initiated On, N (%)					
LPV/r + lamivudine + stavudine	0 (0.0)	559 (77.9)	163 (50.5)	108 (55.4)	234 (79.9)
LPV/r + lamivudine + abacavir	211 (96.4)	159 (22.1)	0 (0.0)	0 (0.0)	11 (3.8)
LPV/r + lamivudine + other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.1)
Ritonavir + lamivudine + stavudine	0 (0.0)	0 (0.0)	160 (49.5)	87 (44.6)	39 (13.3)
ATZ/r + lamivudine + abacavir	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	5 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: LPV/r: ritonavir-boosted lopinavir, ATZ/r: ritonavir-boosted atazanavir; PMTCT: prevention of mother-to-child transmission of HIV; SD: standard deviation

Table 3

Characteristics, plasma HIV-1 RNA quantity, CD4 percentage, and weight-for-age Z-score pre-antiretroviral therapy (ART) initiation, and plasma HIV-1 RNA quantity, CD4 percentage, and vital status 6 months post-ART initiation in Cohorts A, B, and C stratified by age at ART initiation (<6 months vs. 6–24 months)

	Cohort A			Cohort B			Cohort C.1		
	Age at ART initiation (months)			Age at ART initiation (months)			Age at ART initiation (months)		
	<6	6–24	P	<6	6–24	P	<6	6–24	P
N	104	115		252	466		102	221	
Characteristics									
Sex, N (%)									
Male	42 (40.4)	62 (53.9)	0.045	114 (45.4)	237 (50.9)	0.165	41 (40.2)	127 (57.5)	0.004
Female	62 (59.6)	53 (46.1)		137 (54.6)	229 (49.1)		61 (59.8)	94 (42.5)	
Age at ART initiation (mo), Mean $\pm$ SD	3.3 $\pm$ 1.3	13.6 $\pm$ 5.4	<0.001	3.8 $\pm$ 1.3	14.1 $\pm$ 5.6	<0.001	4.1 $\pm$ 1.1	12.8 $\pm$ 5.0	<0.001
Pre-treatment									
HIV-RNA quantity (copies/mL), N (%)									
<100000	14 (14.3)	8 (7.6)		25 (13.5)	58 (17.0)		4 (4.7)	21 (10.7)	
100000–750000	23 (23.5)	41 (39.1)	0.036	43 (23.2)	114 (33.3)	0.011	17 (19.8)	61 (31.0)	0.019
750000	61 (62.2)	56 (53.3)		117 (63.2)	170 (49.7)		65 (75.6)	115 (58.4)	
Missing	6	10		67	124		16	24	
HIV-RNA quantity (log copies/mL) ^f , Median (IQR)	6.2 (5.4, 6.8)	5.9 (5.6, 6.4)	0.196	6.1 (5.6, 6.5)	5.9 (5.2, 6.3)	<0.001	5.9 (5.9, 5.9)	5.9 (5.5, 5.9)	0.001
CD4 percentage, Mean $\pm$ SD	26.6 $\pm$ 13.4	18.8 $\pm$ 10.4	<0.001	22.9 $\pm$ 11.8	17.4 $\pm$ 8.7	<0.001	23.0 $\pm$ 9.6	16.4 $\pm$ 8.1	<0.001
CD4 percentage, N (%)									
<10	11 (10.8)	21 (18.9)		24 (13.0)	67 (18.3)		8 (8.3)	47 (22.6)	
10–15	14 (13.7)	19 (17.1)	0.153	17 (9.2)	89 (24.3)	<0.0001	13 (13.5)	48 (23.1)	<0.001
15	77 (75.5)	71 (64.0)		143 (77.7)	210 (57.4)		75 (78.1)	113 (54.3)	
Missing	2	4		68	100		6	13	
Weight-for-age z-score (WAZ), Mean $\pm$ SD	−1.99 $\pm$ 2.0	−2.39 $\pm$ 1.8	0.127	−2.55 $\pm$ 1.8	−2.63 $\pm$ 1.7	0.638	−2.54 $\pm$ 1.8	−2.47 $\pm$ 1.7	0.753

	Cohort A			Cohort B			Cohort C.1		
	Age at ART initiation (months)	6–24	P	Age at ART initiation (months)	6–24	P	Age at ART initiation (months)	6–24	P
WAZ <-2, N (%)	48 (47.1)	70 (63.1)	0.019	107 (60.1)	238 (64.2)	0.402	52 (58.4)	117 (58.2)	0.972
Missing	2	4		75	95		13	20	
6 months post-ART initiation									
Time since treatment start of 6 month HIV-RNA quantity (mo), Mean $\pm$ SD	5.7 $\pm$ 1.3	5.6 $\pm$ 1.3	0.702	6.3 $\pm$ 1.8	6.2 $\pm$ 1.8	0.872	6.0 $\pm$ 1.3	5.8 $\pm$ 0.9	0.073
HIV-RNA quantity (copies/mL), N (%)									
<50	18 (31.0)	5 (9.8)		77 (40.1)	152 (44.2)		22 (26.5)	76 (39.2)	
50–1000	16 (27.6)	12 (23.5)	0.05	57 (29.7)	103 (29.9)	0.78	39 (47.0)	70 (36.1)	0.20
1000–100000	16 (27.6)	22 (43.1)		23 (12.0)	38 (11.1)		14 (16.9)	27 (13.9)	
100000–750000	2 (3.5)	4 (7.8)		12 (6.3)	18 (5.2)		6 (7.2)	19 (9.8)	
750000	6 (10.3)	8 (15.7)		10 (5.2)	12 (3.5)		2 (2.4)	2 (1.0)	
Missing	46	64		60	122		19	27	
HIV-RNA quantity (log copies/mL), Median (IQR)	2.8 (1.59, 4.18)	3.5 (2.33, 4.93)	0.025	2.3 (1.6, 3.6)	2.2 (1.6, 3.1)	0.176	2.6 (1.7, 3.2)	2.2 (1.7, 3.0)	0.176
CD4 percentage, Mean $\pm$ SD	31.1 $\pm$ 10.0	24.6 $\pm$ 9.1	<0.001	28.3 $\pm$ 9.4	25.3 $\pm$ 8.7	<0.001	28.3 $\pm$ 10.2	26.1 $\pm$ 9.3	0.086
CD4 percentage, N (%)									
<10	1 (1.7)	0 (0.0)		4 (2.2)	14 (4.2)		3 (3.8)	5 (2.6)	
10–15	2 (3.4)	5 (10.9)	0.218	11 (5.9)	26 (7.9)	0.313	6 (7.5)	17 (8.9)	0.829
15	56 (94.9)	41 (89.1)		171 (91.9)	291 (87.9)		71 (88.8)	170 (88.5)	
Missing	45	69		66	135		22	29	
Vital status, N (%)									
Alive	88 (88.9)	83 (79.8)	0.076	204 (95.8)	375 (97.2)	0.370	81 (89.0)	189 (90.9)	0.618
Dead	11 (11.1)	21 (20.2)		9 (4.2)	11 (2.9)		10 (11.0)	19 (9.1)	
Missing	5	11		39	80		11	13	

Note: Assay to assess HIV-RNA quantity in Cohort C.1 used an upper limit of detection of 750,000 copies/mL, which led to truncation of more than half of the measurements.

Abbreviations: SD: standard deviation